Supplementary Information

Equations for a PK model of denosumab [14]

$$\frac{dA_D}{dt} = -k_a \cdot A_D$$

$$\frac{dA_{tot}}{dt} = k_a \cdot A_D - CL_{tot} \cdot C - Q \cdot \left(C - \frac{A_P}{V_2} \right)$$

$$\frac{dA_P}{dt} = Q \cdot \left(C - \frac{A_P}{V_2} \right)$$

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{\deg} \cdot R_{tot} - \frac{\left(k_{\text{int}} - k_{\deg}\right) \cdot R_{tot} \cdot C}{K_{SS} + C}$$

where

$$CL_{tot} = CL_{lin} + \frac{k_{\text{int}} \cdot V_1 \cdot R_{tot}}{K_{SS} + C},$$

and

$$C = \frac{1}{2}\left[\left(\frac{A_{tot}}{V_1} - R_{tot} - K_{SS} \right) + \sqrt{\left(\frac{A_{tot}}{V_1} - R_{tot} - K_{SS} \right)^2 + 4 \cdot K_{SS} \cdot \frac{A_{tot}}{V_1}} \right].$$

A_D is the amount of denosumab in the subcutaneous depot compartment, A_{tot} the total amount of denosumab in the central compartment, A_P the amount of denosumab in the peripheral compartment, R_{tot} the total RANKL level (including both free RANKL and RANKL bound to denosumab). CL_{tot} is denosumab total clearance, C the serum free denosumab concentration. k_a is the absorption rate constant, CL_{lin} the denosumab linear clearance, k_{int} the elimination rate constant of drug-target (here denosumab-RANKL) complex, V_1 the volume of distribution in the central compartment, K_{SS} the steady-state constant, Q the intercompartment clearance, V_2 the volume of distribution in the peripheral compartment, k_{syn} the synthesis rate of RANKL, $k_{\deg}$ the degradation rate constant of RANKL.

Composite criterion to select the best reduced model [15]

A final lumped model was selected using the following composite criterion:

$$CC(m,\alpha) = \alpha \cdot T_1(m) + (1-\alpha) \cdot T_2(m)$$

where

$$T_1(m) = \frac{SS(m) - SS(M)}{SS(m_0) - SS(M)}$$

$$T_2(m) = \frac{m - m_0}{M - m_0}.$$

T_1 and T_2 represent model performance and complexity, respectively. m is the number of states in the reduced model, m_0 and M the minimum and maximum number of states, respectively, and $SS(m)$ the sum of squared differences between predictions for BMD from the original and reduced models when the number of states in reduced models is m. The smallest SS for each m was searched using Simulated Annealing*. The two indices (T_1 and T_2) were weighted with a user defined mixing constant $\alpha : (0 \le \alpha \le 1)$. Both indices cover the scale (0, 1) and therefore provide an intuitive approach for the investigator to choose weighting. For any given value of weighting the smallest criterion value will provide the best trade off between complexity and performance. The search for the lumped model was started with $\alpha = 0.5$, and this value was finally determined by qualification of the simplified model based on a visual predictive check (VPC). For this VPC evaluation, the standard error (SE) of the posterior distribution of each denosumab PK parameter was extracted from the original paper [14] and the possible ranges for D(1), $\varphi_{12\text{-}4}$, $\alpha_{7,22}$ (in Table 2 of [11]), and α for $H^{+}_{20,16}$ and $H^{+}_{20,18D}$ (in Table 3 of [11]) in the bone biology model were provided to calculate the missing SE values due to differences between the original and later-published papers [11, 12]. Log-normal distributions were assumed for each parameter. A total of 250 datasets were simulated to create a credible interval of original predictions.

* Goffe, W.L., Ferrier, G.D. & Rogers, J. Global optimization of statistical functions with simulated annealing. J. Econom. 60, 65-99 (1994).

Figure S1 Fitting (a) and extrapolation (b) results of bone mineral density response when using an existing semi-mechanistic model [24].
A vertical dotted line represents 12 months.
CFB, change from baseline.